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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,323	12/04/2003	Michael J. Caplan	2002834-0232	8163

24280 7590 06/02/2006

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,323	CAPLAN, MICHAEL J.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-47* is/are pending in the application.

4a) Of the above claim(s) *37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36, and 38-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/25/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 34-47 are pending.

2. Claim 37 stands withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

3. In view of the amendment filed 3/14/06, the following objection and rejections remains.

4. Claims 35-36 stand objected to as the claims encompass non-elected embodiments.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 34-36, 38-44 and newly added claims 45-47 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses only a composition comprising heat-killed *E. coli* containing therein peanut allergen selected from the group consisting of Ara h1, Ara h2, and Ara h3 encoded by nucleic acid selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, respectively (see page 33 of specification, sequence listing). However, the amount of allergen produced on a per cell basis varied depending on which clone tested. In general, more Ara h3 was produced than Ara h2 and Ara h1. The specification discloses the intended use of the claimed composition is to treat or prevent allergic reactions in a mammalian subject. The specification discloses mice injected with *E. coli* fails to produce any detectable levels of Ara h1 specific IgG which is critical for converting a Th2 immune response to a Th1 immune response as a method of treating or preventing peanut allergy in a subject (See page 34 of specification). Furthermore, mice immunized with *E. coli* that makes Ara h2 produce high levels of IgG1 (indicative of Th2 immune response) and IgG2a (indicative of Th-1 type immune response),

which again fails to modulate the host immune response to peanut allergen Ara h2 toward Th1 type response. Finally, mice immunized with *E. coli* that makes Ara h3 produce high levels of IgG2a (indicative of Th-1 type immune response) and low levels of IgG1 (indicative of Th2 immune response).

The specification does not disclose any composition comprising dead *E. coli* containing therein any one more modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in nature such that the modified allergen has a reduced ability to bind to or cross-linked IgE with wild-type allergen and a pharmaceutically acceptable carrier. The specification does not teach which one or more amino acids within any one or more IgE binding sites of any wild-type allergen to be modified by amino acid substitution, deletion or addition such that when expressed in *E coli*, the modified allergen containing therein in the dead *E coli* has reduced ability to bind to or cross-link IgE. The specification does not teach how to predict which composition comprising which heat-killed *E. coli* is useful for preventing or treating peanut allergy. The specification does not teach how to make any composition comprising dead *E coli* containing therein any one or more modified allergens whose amino acid sequences differ from that of any "wild-type" allergens such as any foods allergen, or any peanut allergens that "occur in nature" such that the modified allergens have a reduced ability to bind to or cross-link IgE as compared to any wild-type allergen and a pharmaceutical acceptable carrier. This is because of the lack of guidance as to which amino acid(s) within the full-length sequence and the corresponding IgE binding site of any naturally occurred allergens to be modified by substitution, deletion, addition and/or combination thereof such that the modified allergens have a reduced ability to bind or crosslinked IgE compared to the naturally occurring wild-type allergens when expressed in *E coli*. Further, the specification does not teach the "portion" containing IgE binding site of all naturally occurring allergen to be deleted. There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Skolnick *et al*, of record, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Fasler *et al*, of record, teach that allergen peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with

alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2 and IFN-γ production which is indicative of Th1 immune response. Fasler *et al.* further teach that substituting a neutral amino acid residue such as Asn at position 173 with either a basic Lysine, which is a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al,* of record, teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al,* of record, teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Kleber-Janke et al, of record, teach the unpredictability of bacterial *E. coli* expressing allergen such as peanut allergens Ara h1, Ara h2, Ara h5 and Ara h6. The amount of allergen expressed in E coli depends on the strain of E coli such as BL21(DE3), the effect of rare codon usage among the peanut allergens (see page 421, col. 2, in particular). Kleber-Janke et al teach Ara h1, Ara h2, and Ara h6 are affected by poor codon usage. Given the unlimited number of undisclosed modified allergen, modified food allergen and modified peanut allergens, it is unpredictable which composition comprising dead *E coli* strain containing any modified allergen would be useful for treating or preventing allergy in mammalian subject.

Even if the allergen is limited to unmodified peanut allergen Ara h1 (SEQ ID NO: 1), Ara H2 (SEQ ID NO: 2) and Ara h3 (SEQ ID NO: 3), immunizing mice with dead *E. coli* contained

therein three different peanut allergens results in three different outcomes. Since the modified allergens contained within the *E coli* is not enabled, it follows that any modified allergen is located in the cytoplasm or periplasm of the dead *E. coli* in the claimed composition is not enabled. It also follows that the composition recited in claims 43-47 is not enabled.

In *re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Applicants' arguments filed 3/14/06 have been fully considered but are not found persuasive.

Applicants' position is that in arguing the immunological properties of the claimed composition, the examiner points to the examples in the specification (specifically, Examples 3 and 4) and attempts to ague that these examples show unpredictability because different results were obtained with different allergens. As discussed in the specification, microorganisms such as *E coli* tend to produce Th1 type (i.e. non-allergic) immune reactions in individuals. In contrast, allergens such as the peanut allergens Ara h1, 2, and 3 tend to produce Th2-type response. According to the Examples, high levels of IgG2a (indicative of a Th1-type response) were observed for both Ara h2 and Ara h3. High levels of IgG1 (indicative of a Th2-type response) were also observed for Ara h2. It is true that evidence of a Th2-type reaction was also observed for Ara h2, but that was explained as resulting from released protein which, obviously, would be expected to induce a strong Th2 response. Far from demonstrating unpredictability of protein allergen expression, Kleber-Janke et al shows that at the time of filling, researchers of ordinary skill in the art at their disposal a variety of tools that could be employed to predictably modulate expression as desired. The current application describes a vast number of Ara h1, 2 and 3 mutations that did reduce IgE binding exemplified in US Serial No. 09/141,220.

In response, the claimed compositions comprise dead *E coli* that contain any modified allergens with reduced IgE binding. One of the issues in the rejection is whether the specification teaches the structure of any one or more modified allergen whose amino acid differs from that of any wild-type allergen, any wild type allergens found in foods such as peanut, milk, eggs, seafood, nuts, diary products, and fruit that occurs in nature without the amino acid sequence

contained in the dead E coli in the claimed composition. The specification does not teach which one or more amino acids within the IgE binding sites of any wild-type allergens found in nature to be deleted, substituted for which amino acids, or added such that the modified allergen expressed in *E coli*, and then rendered dead by heat, or chemical treatment in a composition that is effective for treating allergy by switching a Th2 to a Th1 immune response.

The unpredictability of the modified allergens such as peanut is evidence in the teachings of Fasler *et al,* Burks *et al, and* Stanley *et al.* Fasler *et al* teach that allergen peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2 and IFN-γ production which is indicative of Th1 immune response. Fasler *et al.* further teach that substituting a neutral amino acid residue such as Asn at position 173 with either a basic Lysine, which is a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

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Stanley *et al* teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Given the unlimited number of modified allergen expressed in *E. coli* as a pharmaceutical composition for treating allergy, it is unpredictable which

composition comprising dead E coli containing therein any modified allergen would resulted in a Th1 immune response.

The other issue is whether the modified allergens expressed in *E coli* and rendered dead in the claimed composition produces a Th1 immune response in vivo as a method of treating allergy. As evidence by the teachings of the specification, it is not predictable administering which dead *E. coli* expressing modified peanut allergens Ara h1, Ara h2 and Ara h3 produce a Th1 immune response in vivo. Given the unlimited number of modified allergen having one or more mutations and the lack of guidance as to predict which modified allergen expressed in E coli induces a Th1 immune response, undue amount of experimentation would be required to practice the claimed invention.

With regard to the argument of incorporation by reference, the teachings of US Serial No. 09/141,220 is not available to the public because an application for patent may or may be issued as a patent.

7. Claims 34-36, 38-44 and newly added claims 45-47 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for any and all composition comprising *dead E. coli* containing therein at least any one or more modified allergen, any modified allergen such as any modified food allergen, any modified allergen from peanut, milk, eggs, seafood, nuts, dairy products, fruit, any modified peanut allergen whose amino acid sequence differs from the naturally occurring wild-type allergen that occurs in nature having one or more amino acid deletions, substitution, or addition within any IgE binding site, such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen; and a pharmaceutically acceptable carrier.

The specification discloses only a composition comprising heat-killed *E. coli* containing therein peanut allergen selected from the group consisting of Ara h1, Ara h2, and Ara h3 encoded by nucleic acid of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, respectively (see page 33 of specification, sequence listing). However, the amount of allergen produced on a per cell basis varied depending on which clone tested. In general, more Ara h3 was produced than Ara h2 and Ara h1. The specification discloses the intended use of the claimed composition is to treat or

prevent allergic reactions in a mammalian subject. The specification discloses mice injected with *E coli* fails to produce any detectable levels of Ara h1 specific IgG which is critical for converting a Th2 immune response to a Th1 immune response as a method of treating or preventing peanut allergy in a subject (See page 34 of specification). Furthermore, mice immunized with *E. coli* that makes Ara h2 produce high levels of IgG1 (indicative of Th2 immune response) and IgG2a (indicative of Th-1 type immune response), which again fails to modulate the host immune response to peanut allergen Ara h2 toward Th1 type response. Finally, mice immunized with *E. coli* that makes Ara h3 produce high levels of IgG2a (indicative of Th-1 type immune response) and low levels of IgG1 (indicative of Th2 immune response).

The specification does not describe the structure corresponding with function of any modified allergen in the claimed composition. There is a lack of a written disclosure about the structure of any and all modified allergen, modified allergen such as any modified food allergen, any modified peanut allergen whose amino acid sequence is identical to that of said allergen protein as it occurs in nature except that at least one or more amino acids have been deleted, substituted, added within any IgE binding site so that the modified protein has a reduced ability to bind and crosslink IgE antibodies. Without the amino acid sequence of any modified allergen or food allergen in the claimed composition, the specification merely ask one of skilled in the art to come up with the structure of the modified allergen in the dead *E coli* for the claimed composition. Since the modified allergens contained within the *E coli* is not adequately described, it follows that any modified allergen is located in the cytoplasm or periplasm of the dead *E. coli* in the claimed composition is not adequately described. It also follows that the composition recited in claims 43-47 comprising any modified allergen in *E coli* is not adequately described.

Further, given the lack of a written description of *any* additional representative species of modified food allergens other than the specific modified peanut allergens expressed in *E coli* as encompassed by the claimed composition, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/14/06 have been fully considered but are not found persuasive.

Applicants' position is that while modified allergens other than peanut allergens were not reduced to practice these species were described in the specification (see [0017], [0019], [0062]-[0072] and Appendix A). A number of these allergens IgE binding epitopes were already known. For others they could be identified using routine methods (e.g., page 7, line 31 to page 8, line 8 and Example 1 of incorporated U.S. Serial No. 09/141,220, see [0069].

In response, the claimed compositions comprise dead *E coli* that contain any modified allergens with reduced IgE binding. The specification at [0017], [0019], [0062]-[0072] and Appendix A merely extends an invitation to one of ordinary skill in the art to come up with the structure of modified allergen or modified food allergen and expressed in *E coli.* for the claimed composition.

The specification does not reasonably provide a **written description** for any and all composition comprising *dead E. coli* containing therein at least any one or more modified allergens, any modified allergen such as any modified food allergen, any modified allergen from peanut, milk, eggs, seafood, nuts, dairy products, fruit, any modified peanut allergen whose amino acid sequence differs from the naturally occurring wild-type allergen that occurs in nature having one or more amino acid deletions, substitution, or addition within any IgE binding site, such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen; and a pharmaceutically acceptable carrier.

The specification does not adequate describe the structure of any modified food allergens whose amino acid sequence differs from that of wild-type sequence without the amino acid sequence in the claimed composition. The issue here is not whether the modified allergens could be identified using routine method, the issue here is written description of the modified allergens. Without the amino acid sequence of the modified allergens or the corresponding nucleic acid, applicants merely ask one of ordinary skill in the art to come up with the structure of the modified allergens contained in the dead *E. coli* for the claimed composition. As discussed above, incorporating the teachings of a U.S. Serial number U.S. Serial No. 09/141,220 is not incorporating the teachings of a patent or publication. An application for patent may or may not be issued as a patent. Therefore, the teachings are not available to the public.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 34-36, 38-40, and 42-45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,888,799 (of record, March 1999, PTO 1449) in view of WO 99/38978 publication (of record, Aug 1999, PTO 1449) and Yeung et al (of record, J Immunology 161: 4146-4152, 1998; PTO 892).

The '799 patent teaches a composition comprising live bacteria such as *E. coli* K-12 containing therein any allergen and a pharmaceutically acceptable carrier to the mucosal immune system (See entire document, col. 2, line 25-34, col. 7, line 53, col. 9, lines 59-67, in particular). The reference allergen is located in the periplasm (See column 14, lines 31-35, in particular). The reference microorganism such as *E. coli* K-12 have the advantages of (1) being avirulent (derivative of a pathogenic strain) and do not exchange genetic material with the pathogenic strains, (2) useful as delivery vehicle to stimulate the host cellular response such as the production of IgA in the secretory pathway with a concomitant stimulation of the humoral and cellular immune response (See column 2, lines 60-64, column 5, Table 1, in particular).

The claimed invention as recited in claim 34 differs from the teachings of the reference only in that the composition comprising dead *E coli* containing therein at least one modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in nature such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the non-modified allergen.

The claimed invention as recited in claim 35 differs from the teachings of the reference only in that the composition comprising dead *E coli* containing therein modified allergen found in foods.

The claimed invention as recited in claim 36 differs from the teachings of the reference only in that the composition comprising dead *E coli* containing therein modified allergen found in peanuts.

The claimed invention as recited in claim 38 differs from the teachings of the reference only in that the composition comprising dead *E coli* containing therein modified allergen found in Ara h1 (SEQ ID NO: 1), Ara h2 (SEQ (ID NO: 2) or Ara h3 (SEQ ID NO: 3).

The claimed invention as recited in claim 39 differs from the reference from the teachings of the reference only in that the composition dead *E coli* containing therein modified allergen whose amino acid sequence differs from the sequence of wild-type allergen by one or more amino acid amino acid deletions, substitution, or addition within an IgE binding site of the wild-type peanut allergen.

The claimed invention as recited in claim 40 differs from the reference from the teachings of the reference only in that the composition dead *E coli* containing therein modified allergen lacks a portion of the wild-type allergen within said portion includes IgE binding site.

The WO 99/38978 publication teaches a composition comprising live *E coli* containing therein at least one peanut allergen such as Ara h1, Ara h2 and Ara h3 where the amino acids within each of the binding sites have been substituted such that the modified allergens have reduced IgE binding compared with the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, in particular). The reference further teaches a method comprising the steps of providing a composition comprising a modified allergen such as peanut protein Ara h1, Ara h2, Ara h3 or a portion thereof wherein the protein or portion thereof has at least one amino acid has been deleted or substituted such that the modified protein has a reduced ability to bind and crosslink IgE antibodies (See Abstract, page 19, reference SEQ ID NO: 2, 4 and 6, claims 14, 17-20, 23 and 36 of WO 99/38978 publication, in particular). The reference modified peanut allergen is expressed or produced in a recombinant host such as bacteria wherein the allergen is secreted into the periplasma space since the bacterial cells must be lysed in denaturing binding buffer (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular). The WO 99/38978 publication further teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE

binding and substitution of a specific single amino acid within each of the identified epitope abolishes IgE binding (See abstract, page 18, Table 4, Table 5 and Table 6, in particular).

Yeung et al teach heated-killed bacteria such as listeria monocytogenes has innate adjuvant activity to provoke TH1 dominated immune response in treatment of allergy (see page 4146, col. 1, in particular). Yeung et al further teach heat-killed bacteria rather than live bacteria are effective in reducing antigen/allergen specific IgE synthesis (see page 4151, col. 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute live *E coli* comprising allergen as taught by the '799 patent for the lived *E coli* comprising modified peanut allergens such as Ara h1, Ara h2, Ara h3 or a portion thereof that has a reduced ability to bind and crosslink IgE antibodies as taught by the WO 99/38978 publication and then heat-killed it and use it as a composition to promote Th1-dominated immune response as taught by Yeung et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 99/38978 publication teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and the modified peanut allergens are useful for a method of treating a subject susceptible to an anaphylactic reaction (allergic reaction) to peanut allergen (See abstract, in particular). It is within the purview of one ordinary skill in the immunology art to heat-killed microorganism such as *E coli* as a vaccine as taught by the '799 patent or (see col. 1, lie 52-57, in particular) and serve as an adjuvant as taught by Yeung et al. Claim 43 is included in this rejection because it is obvious that the modified allergen cannot be detected by antibody binding without disrupting the dead *E coli* since the modified allergen is located within the periplasm and not secreted as taught by the '799 patent. Claim 44 is included in this rejection because it is within the purview of one ordinary skill in the pharmacology art to administer the formulation by rectal administration. The recitation of "dead" *E coli* is an obvious variation of live *E coli* taught by the references teachings.

Applicants' arguments filed 3/14/06 have been fully considered but are not found persuasive.

Applicants' position is that WO 99/38978 publication relates to peanut allergens and goes to great lengths to highlight the potentially lethal consequences of accidental exposure to these anaphylactic allergens (see page 14, line 11). In contrast, the '799 patent relates for most part to methods of expressing isolated microbial antigens (e.g., antigens from infectious bacteria or viruses) in avirulent microbial vehicles. These so-called "subunit vaccines" are designed to minimize unwanted immune reactions while providing protection against infectious pathogens. In addition, even though the expressed antigens in the cited references are sometimes described in terms that include allergens, anaphylactic allergens are never discussed. The potent immunological nature of anaphylactic peanut allergens would discourage one of ordinary skill in the art to substitute them into methods that have only been described fro tamer antigens such as isolated microbial antigens and non-anaphylactic allergens. With regard to heat-killing step, the teachings of Yeung are not generalized to all bacteria as the examiner suggested. There is no teachings or suggestion of incorporating KLH or other antigen within heat-killed Listeria monocytogenes. Yeung does not teach anything about bacteria generally – the teachings are limited to *Listeria*. One of ordinary skill in the art would have had very little motivation to make the substation, let alone the expectation that the substitution would lead to successful methods of treating allergies to the anaphylactic allergens. The examiner's obviousness arguments are based on improper hindsight reconstruction.

In response to applicants' argument that the '799 patent does not teach expressing anaphylactic allergens, the WO 99/38978 publication teaches expressing anaphylactic modified allergens such as Ara h1, Ara h2 and Ara h3 in live *E. coli* (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, in particular). The use of *E. coli* as a vehicle containing therein any allergen is well known in the art at the time the invention made as taught by the '799 patent (See entire document, col. 2, line 25-34, col. 7, line 53, col. 9, lines 59-67, in particular). The use of live bacteria expressing allergen is known in the art as taught by the '799 patent. The use of "dead" bacteria as a vaccine is also well known in the art as evidence by the teachings of Yeung et al. The advantage of heat-killed bacteria rather than live bacteria is that it is effective in reducing antigen/allergen specific IgE synthesis (see page 4151, col. 1, in particular). In response to applicants' argument that the adjuvant effect can be generalized to other bacteria, the term "adjuvant effect" is not recited in the claims. Further, the '799 patent teaches the use of bacteria *E coli* expressing allergen. The adjuvant effect of bacteria would have been an inherent property given that all *E coli* expressed lipopolysaccharide (LPS) on its membrane.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the teachings of the '799 patent pertaining to a composition comprising live bacteria such as *E. coli* K-12 containing therein any allergen and a pharmaceutically acceptable for treating allergy, the teachings of the WO 99/38978 publication pertaining to modified anaphylactic food allergens such as Ara h1, Ara h2 and Ara h3 in live *E. coli* and the teachings of the teachings of Yeung et al pertaining to heat-killed bacteria is effective in reducing antigen/allergen specific IgE synthesis (see page 4151, col. 1, in particular) would have lead of ordinary skill in the art at time the invention was made with the expectation of success to heat-killed any bacteria as taught by Yeung using the lived *E. coli* expressing modified food allergens in the composition as taught WO 99/38978 publication or substituting the lived *E. coli* K12 expressing any modified allergen and then heat killed the E coli expressing the desired modified allergen as a pharmaceutical composition for treating allergen as taught by the '799 patent and Yeung et al. The strongest rationale for combining references is a recognition in the art that some advantage or expected beneficial result would have been produced by their combination. This recognition may be an expressed statement in a reference, an implication that can be drawn from one or more references or a convincing line or reasoning based upon established principles or legal precedent.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971).

11. Claim 41 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,888,799 (of record, March 1999, PTO 1449) in view of WO 99/38978 publication (of record, Aug 1999, PTO 1449) as applied to claims 34-36, 38-40, and 42-44 above, and further in view of US Pat No. 5,834,246 (of record, Nov 1998, PTO 892).

The combined teachings of the '799 patent, the WO 99/38978 publication and Yeung et al have been discussed supra.

The claimed invention in claim 41 differs from the teachings of the references only in that the food allergen protein is located in the cytoplasm of the dead *E coli*.

The '246 patent teaches a recombinant system for inducible overexpression of protein such as cholera B-subunit (CTB) with TtacP promoter in *E. coli*. The expression or production of the reference protein CTB is inducible under the control of the reference TtacP promoter and this allows production of high levels of CTB in *E. coli* harboring these plasmids (See column 3, lines 30-39, column 4, Example 1, column 5, lines 63 bridging column 6 lines 1-54, Table 1, in particular). The '246 patent further teaches the recombinant protein CTB is secreted to the cytoplasm when produced by V. cholerae and then readily be purified in high yield from the culture supernatants (See column 7, lines 43-46, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TtacP promoter for inducible expression of protein at high levels in *E. coli* as taught by the '246 patent for conventional promoter as taught by the '799 patent to produce modified peanut allergens such as Ara h1, Ara h2, Ara h3 or a portion thereof in the cytoplasm as taught by the '246 patent that has a reduced ability to bind and crosslink IgE antibodies as taught by the WO 99/38978 publication and heat killed the *E coli* for a composition comprising dead *E coli* containing modified peanut allergen located in the cytoplasm of the dead E coli as taught by the '799 patent, the WO 99/38978 publication, Yeung et al and the '246 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '246 patent teaches that the TtacP inducible promoter has the advantages of (1) producing the protein of interest at high level without affecting the growth of the microorganisms (See column 3, lines 30-39, column 4, Example 1, column 5, lines 63 bridging column 6 lines 1-54, Table 1, in particular) and (2) the recombinant protein is secreted

into the cytoplasm when produced by microorganism such as V. cholerae which then readily be purified in high yield from the culture supernatants (See column 7, lines 43-46, in particular).

Applicants' arguments filed 3/14/06 have been fully considered but are not found persuasive.

Applicants' position is that the '246 patent does not point to the teachings in the '978 patent that the allergen is located within the cytoplasm.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. The '246 patent teaches the recombinant protein is secreted to the cytoplasm (See column 7, lines 43-46, in particular). Further, the '799 patent teaches allergen is located in the periplasm, which is part of the cytoplasm (See column 14, lines 31-35, in particular). Finally, the WO 99/38978 publication teaches expressing anaphylactic modified allergens such as Ara h1, Ara h2 and Ara h3 in *E. coli* wherein the reference allergens are obviously located in the cytoplasm since the allergens in the composition are made using the same strain of *E. coli* and same expression vector as the specification (see WO 99/38978 at page 16, synthesis and purification of recombinant Ara h2 protein, in particular).

12. The following new grounds of objection and rejections are necessitated by the amendment filed 3/14/06.

13. The disclosure is object to because of the following informality: "**March** 6, 2000" at page 1, line 7 should have been "**April** 6, 2000". Correction is required.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

15. Claims 38 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "SEQ ID NO: 1", "SEQ ID NO: 2" and "SEQ ID NO: 3" in claim 38 has no antecedent basis in base claim 34 because base claim 34 requires amino acid sequence whereas

"SEQ ID NO: 1", "SEQ ID NO: 2" and "SEQ ID NO: 3" are nucleic acid sequences encoding the wild-type allergen Ara h1, Ara h2, and Ara h3, respectively.

The plural "alcohols" in claim 47 is inconsistent with a singular chemical treatment recited claim 47. It is suggested that claim 47 be amendment to recite "...alcohol."

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,888,799 (of record, March 1999, PTO 1449) in view of WO 99/38978 publication (of record, Aug 1999, PTO 1449) and Yeung et al (of record, J Immunology 161: 4146-4152, 1998; PTO 892) as applied to claims 34-36, 38-40, and 42-44 above, and further in view of

The combined teachings of the '799 patent, the WO 99/38978 publication and Yeung et al have been discussed supra.

The claimed invention in claim 46 differs from the teachings of the references only in that composition wherein the *E coli* was skilled by chemical treatment.

The claimed invention in claim 47 differs from the teachings of the references only in that composition wherein the *E coli* was skilled using a chemical selected from the group consisting of iodine, bleach, ozone, and alcohols.

The '723 patent teaches various methods such as heat (see col. 1, lines 15-30, col. 7, line 17-30, col. 11, line 66, in particular), chemical treatment such as alcohols (see col. 1, line 21, in

particular), bleach (see col. 10, line 39-40, in particular) or pressure sterilization (ozone) to kill, or inactivate bacteria such as *E coli* (see col. 11, lines 42-67, col. 15, line 8, in particular). The '723 patent teaches these methods can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to kill any *E. coli* expressing modified allergen as taught by the '799 patent, the WO 99/38978 publication and Yeung et al by means of chemical treatment as taught by the '723 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because a successful vaccine preparation method should ideally resulted in a high degree of bacteria inactivation while maintaining its ability to stimulate a protective immune response and these methods can improve the safety of vaccine or any product used by patient as taught by the '723 patent (see col. 8, lines 26-67, col. 9, lines 1-15, in particular).

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The

examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

22. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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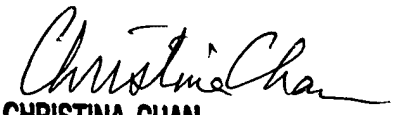
May 26, 2006



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